REMARKS

I. The Invention

The present invention resides in the novel strategy of *ex vivo* preparation of a tumor-specific vaccine based on the use of bispecific antibodies, which are heterologous intact antibodies of certain isotype and subclass combinations. By virtue of its specificities for a tumor-associated antigen, a T cell receptor, and an Fc receptor, a bispecific antibody of the present invention simultaneously binds to a tumor cell (an autologous tumor cell that is extracted from a patient and bears a tumor-associated antigen of endogenous source), a T cell, and an Fc receptor-positive effector cell. An enhanced tumor-specific immunity is achieved following the recruitment of T lymphocytes and Fc receptor-bearing effector cells to the tumor cells and the subsequent activation of the T cells and effector cells.

II. Status of the Claims

Claims 1-26 were originally filed, and claims 27-30 were later added. Subsequently, claim 27 was canceled. Claims 1-8, 13-21, 23, and 26 were pending under examination.

Upon entry of the present amendment, claims 17 and 18 are amended to recite "step (d)" instead of "step (c)" to ensure proper antecedent basis. Claims 23 and 26 are amended to recite "an antibody-tumor cell preparation" to replace "a tumor cell preparation." This amendment finds support in claim 1. Claim 23 is further amended to improve clarity and ensure proper antecedent basis. New claims 31-35 are added, which recite either a pharmaceutical composition comprising activated peripheral blood mononucleated cells or a method for preventing tumor recurrence comprising the step of administering activated peripheral blood mononucleated cells. The administration of activated peripheral blood mononucleated cells is supported by the specification, *e.g.*, on page 26, lines 15-17, and page 7, lines 7-24. More specifically, new claims 31 and 32 are supported by claims 26 and 14, and claims 23 and 14, respectively; new claims 33 and

34, reciting addition of the peripheral blood mononucleated cells following a preincubation of the inactivated tumor cells with the heterologous bispecific antibodies, are supported by the specification as originally filed, *e.g.*, in the bridging paragraph between pages 11 and 12; and new claim 35 is supported by claims 26 and 31-34. The present amendment adds no new matter.

III. Claim Rejections

A. Double Patenting Rejection over U.S. Patent No. 6,551,592

Claims 23 and 26 were rejected under the judicially created doctrine of the obviousness-type of double patenting over claims 1-13 of U.S. Patent No. 6,551,592 ("the '592 patent"). The Examiner also stated that claims 23 and 26 are obvious over the '592 patent in view of Volker *et al.* (U.S. Patent No. 5,911,987) and required Applicants to show a common ownership between the present application and the '592 patent. Because it is unclear to Applicants whether the rejection is based on the judicially created doctrine of obviousness-type of double patenting, which can be resolved by a terminal disclaimer but not a common ownership, or based on 35 U.S.C. §103(a), which can be resolved by a common ownership, Applicants will address these two possibilities separately in the sections below.

1. Nonstatutory Obviousness-Type of Double Patenting

According to MPEP §804, an obviousness-type of double patenting rejection is appropriate when the claimed invention is an obvious variation of the invention claimed in a patent. A double patenting rejection of the obviousness-type is analogous to a failure to meet the nonobviousness requirement under 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art under §103. Thus, Applicants will analyze claims 23 and 26 in light of claims 1-13 of the '592 patent and Volker *et al.* in the same manner as for an obviousness determination under §103(a).

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such combination. MPEP §2143.

Claim 23 as amended is drawn to a method for preventing the recurrence of a tumor by administering to an individual an antibody-tumor cell preparation prepared according to claim 1. Claim 26 as amended is drawn to a pharmaceutical composition comprising such an antibody-tumor cells preparation. The method of claim 1 contains the following limitations:

1. the method comprises the steps of:

a) isolating autologous tumor cells;

b) treating the tumor cells to prevent the survival thereof following reinfusion;

c) incubating the thus treated tumor cells with intact heterologous bispecific antibodies showing the following properties:

(i) binding to a T cell;

(ii) binding to at least one tumor-associated antigen on a tumor cell;

(iii) binding, by their Fc portion to Fc receptor-positive cells; and

(iv) capable of activating the Fc receptor-positive cell whereby the expression of cytokines, co-stimulatory antigens or both is induced or increased; and

2. the bispecific antibodies have specifically enumerated isotype combinations.

Claims 1-13 of the '592 patent are drawn to a method of treatment of a human or animal subject suffering from a tumor disease consisting of administering to

said subject an effective amount of an intact heterologous bispecific antibody, which is of specifically enumerated isotype combinations and has the following properties:

(a) binding to a T cell and activating said T cell;

(b) binding to tumor-associated antigens on a tumor cell;

(c) binding, through its Fc portion to the Fc receptor of Fc receptor-positive cells;

(d) activation of said Fc receptor-positive cell by said binding of said antibodies to the Fc receptor-positive cell and, thereby initiating or increasing the expression of cytokines and/or co-stimulatory molecules; and

(e) inducing a physiological activation of the T cell by a member selected from the group consisting of co-stimulatory molecules and cytokines, this activation being indicated by up-regulation of activation markers, killing of the tumor cell, T cell proliferation or a combination thereof, inducing anti-tumor immunity.

The Volker *et al.* reference discloses methods for inducing an enhanced anti-tumor immunity and for producing a tumor-specific vaccine. These methods require the initial step of antigenizing the tumor cells with an antigen of exogenous origin, *e.g.*, viral protein hemagglutinin-neuraminidase (HN) expressed on the tumor cell surface following the transfection of the tumor cells with the Newcastle Disease Virus (NDV). A bonding agent with dual-specificity, one for the exogenous antigen on the tumor cell surface (such as a viral protein) and the other for a molecule on an effector cell surface (such as CD2 or CD3 on a T cell), is then used to bring the effector cell into close contact with the tumor cell and achieve increased immunogenicity of the tumor cells.

Applicants contend that no *prima facie* showing of obviousness has been established. More specifically, there is no suggestion or motivation, express or implied, that can be found in the claims of the '592 patent or Volker *et al.* for one of skill in the art to combine the elements of the references. Claims 1-13 of the '592 patent do not related

to isolating tumor cells from a patient, inactivating the tumor cells, and preparing an antibody-tumor cells preparation for administration back into the patient. There is no specific suggestion that the use of the bispecific antibodies in combination with any other components. On the other hand, although Volker *et al.* teach an *ex vivo* preparation of tumor cells and multi-specific bonding agents, there is no specific suggestion for the use of any bispecific antibodies of the specified isotype combinations. According to the MPEP, a suggestion or motivation to combine must be one that is specific. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the references also suggest the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). The fact that making the combination to reach the claimed invention may be within the capability of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. MPEP §2143.01. The Examiner has not pointed out anywhere in claims 1-13 of the '592 patent that describes the advantages of administering an antibody-tumor cell mixture prepared *ex vivo* for reinfusion into a patient. Nor has the Examiner pointed out anywhere in the Volker reference that teaches the advantages of a bispecific antibody of certain isotype combinations for use in the *ex vivo* preparation of an antibody-tumor cell mixture for the purpose of inducing anti-tumor immunity. Thus, no specific suggestion or motivation to combine has been identified under the MPEP guideline.

Furthermore, there is no reasonable expectation of success in combining the claim elements either. Because the effect and efficacy of antibody-based treatment methods can vary significantly, depending the mode of administration of the antibodies (*e.g.*, direct administration of antibodies or administration of antibodies following *ex vivo* incubation with tumor cells), which relates to the duration of the antibodies' presence before degradation, and the isotype combinations of multi-specific antibodies, which relates to the proper cross-signaling of T cells and other immune effector cells, one cannot reasonably expect, without the benefit of extensive experimentation, that simply combining the subject matter of claims 1-13 of the '592 patent and the Volker reference

would result in a successful therapeutic method for inducing a specific anti-tumor immune response in a patient.

As such, claims 23 and 26 have not been shown to be *prima facie* obvious over claims 1-13 of U.S. Patent No. 6,551,592 in view of Volker *et al.*

2. Obviousness Rejection under 35 U.S.C. §103(a)

If the obviousness rejection of claims 23 and 26 was made based on 35 U.S.C. §103(a) over the '592 patent in view of Volker *et al.*, Applicants contend that the '592 patent is not available to form the basis of such an obviousness rejection. As set forth in 35 U.S.C. §103(c), subject matter developed by another person, which qualifies as prior art only under §102(e), (f), or (g), shall not preclude patentability under 35 U.S.C. §103(a) where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. In the instant case, the '592 patent and the present application were all assigned to or obligated to be assigned to the same entity: GSF Forschungszentrum fur Umwelt und Gesundheit GmbH (Ingolstadter, DE), at the time the present invention was made. Accordingly, no §103(a) rejection of the pending claims can be properly based on the '592 patent in view of Volker *et al.*

Moreover, even if the '592 patent were available as a prior art reference for the purpose of supporting an obviousness rejection under 35 U.S.C. §103(a), the discussion in the previous section indicates that the present invention as defined by claims 23 and 26 still would not be obvious over the combination of the '592 patent and Volker *et al.* A rejection under 35 U.S.C. §103(a) would thus be improper nevertheless.

3. Summary

As discussed above, at the time the present invention was made, it was assigned to or under the obligation to be assigned to the assignee of the '592 patent, GSF Forschungszentrum fur Umwelt und Gesundheit GmbH. The '592 patent is therefore not

available as a prior art reference to form the basis of a 35 U.S.C. §103(a) obviousness rejection, a §103(a) obviousness rejection is not proper. Furthermore, the present invention is not obvious over claims 1-13 of the '592 patent alone or over the '592 patent in view of Volker *et al.* Therefore, neither a 35 U.S.C. §103(a) obviousness rejection nor a nonstatutory obviousness-type double patenting rejection can be properly sustained.

As such, Applicants respectfully request the withdrawal of the rejection of claims 23 and 26 over claims 1-13 of U.S. Patent No. 6,551,592 in view of Volker *et al.*

B. 35 U.S.C. §112, Second Paragraph

Claims 23 and 26 were also rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner pointed out that the terms "a tumor cell preparation prepared according to the method of claim 1" and "a tumor cell preparation obtained by the method of claim 1" are unclear as to whether they refer to the tumor cell preparation mentioned in the claims, *i.e.*, an inactivated tumor cell sample, or a preparation comprising a mixture of bispecific antibodies with tumor cells.

Claims 23 and 26 have been amended, according to the Examiner's suggestion, to recite "an antibody-tumor cell preparation" in place of the phrase "a tumor cell preparation" in the above-mentioned terms. Applicants submit that this rejection is overcome by this amendment and thank the Examiner for her helpful suggestions.

C. 35 U.S.C. §102

Claims 23 and 26 were further rejected under 35 U.S.C. §102(b) for alleged anticipation by Hanna *et al.* (U.S. Patent No. 5,484,596). Specifically, this anticipation rejection appears to be based on the notion that these claims may be construed as reading on pharmaceutical compositions comprising, and methods of treatment comprising the use of, tumor cell preparations obtained according to claim 1, *i.e.*, isolated and inactivated tumor cells. Since the amended claims 23 and 26 now recite "antibody-tumor cell preparation" instead of "tumor cell preparation" and clearly do not

allow this interpretation, Applicants submit that the anticipation rejection based on Hanna *et al.* is overcome.

D. Provisional Double Patenting Rejection over USSN 10/378,218

Claims 1-8, 13-21, 23, and 26 were provisionally rejected under the judicially created doctrine of the obviousness-type of double patenting over claims 1, 7, 10, 19, 22, and 23 of USSN 10/378,218.

Applicants submit that the Examiner should withdraw the provisional double patenting rejection and allow the claims pending in the present application. According to the MPEP §822.01, "[i]f the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent..." This is precisely the case in the present application, as the only other rejections, the nonstatutory obviousness-type of double patenting rejection, the indefiniteness rejection, and the anticipation rejection, have been overcome in light of the present claim amendment and above discussions. On the other hand, USSN 10/378,218 has not been allowed. Thus, Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection and allow the pending claims in the present application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
60282982 v1